UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/972,741 | 10/05/2001 | Keith Allen | R-723-CIP | 5377 |

7590 12/18/2002

DELTAGEN, INC.
740 Bay Road
Redwood City, CA 94063

| EXAMINER |
|---|
| QIAN, CELINE X |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/972,741 | Applicant(s) ALLEN, KEITH | |
|---|---|---|---|
| | Examiner Celine X Qian | Art Unit 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above claim(s) *11-16,24-44 and 53-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,17-23 and 45-52* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Claims 1-72 are pending in the application.

### *Election/Restrictions*

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the inventions of Groups I-XX are related, and a search of all the groups is not a serious burden. This is not found persuasive because the inventions of Groups I-XX are patentably distinct for the reason set forth of the record mailed on 9/9/02. Although the inventions may be related, a search of one invention is not co-extensive with the search of another. Therefore, a search of all 20 groups in a single application is burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 11-16, 24-44 and 53-72 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-10, 17-23 and 45-52 are currently under examination on merits.

### *Claim Objections*

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim is drawn to a construct comprising a screening marker. Since it's unclear how it is different from the "selection marker," claim 2 fails to limit the subject matter of claim 1.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-10, 17-23 and 45-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous knockout mouse comprising a homozygous disruption in the magnesium-dependent phosphatase gene, wherein there is no functional magnesium-dependent phosphatase produced, and exhibiting phenotypic features including lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold as compared to wild type mice, a method of producing such a transgenic mouse, and a cell isolated from the knockout mouse, does not reasonably provide enablement for other transgenic and/or knockout animal comprising any disruption in any magnesium-dependent phosphatase gene. Further, the specification is not enabling for a knockout mouse comprising any disruption in any magnesium-dependent phosphatase gene and for any cell comprising any disruption in a magnesium-dependent phosphatase gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples;

(f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 5-10, 17-23, 45-52 are drawn to a cell comprising a disruption in a magnesium-dependent phosphatase gene, a non-human transgenic animal comprising a disruption in a magnesium-dependent phosphatase gene, a cell from that transgenic animal, a method of producing the mouse with any disruption in the said gene. Thus, the nature of the invention is directed to transgenic animals and methods of producing said transgenic animals.

Breadth of Claims:

In the instant case, the claims 5-10, 17-23 and 45-52 encompass any transgenic animal containing any disrupted allele for the gene that encodes any magnesium-dependent phosphatase. Further, the claims encompass any knockout mouse comprising any disruption in magnesium-dependent phosphatase gene and exhibiting the phenotypes of lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold as compared to wild type mice. Further, the claims encompass any cell comprising any disruption in a magnesium-dependent phosphatase gene and encompass all cells capable of undergoing homologous recombination. The disruption, as disclosed in the specification (page 7, lines 4-14) includes any insertion, deletion or substitution in any portion of the gene (introns, exons, regulatory regions). The claims, therefore, encompass all such disruptions and also cover all animals that contain magnesium-dependent phosphatase gene disruption (page 7, lines 18-25).

The specification does not provide an enabling disclosure for the full scope of transgenic animals of the type claimed. The only embodiment enabled by the specification within the scope of claims 5-10, 17-23 and 45-52 is for a homozygous knockout mouse comprising a disruption in the magnesium-dependent phosphatase gene that results in loss of function of the magnesium-dependent phosphatase and exhibiting phenotypic features such as lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold as compared to wild type mice, a method of producing such a transgenic mouse. Thus the breadth of the claims is very broad and encompasses any transgenic animal and a knockout mouse with any disruption in any magnesium-dependent phosphatase gene and includes any and all mutant forms, substitutions, deletions, or insertions in any magnesium-dependent phosphatase gene (see page 7, lines 24-30, page 8, lines 1-2).

Amount of guidance in the specification and Working Examples:

The specification discloses the use of a specific magnesium-dependent phosphatase gene in producing a homozygous transgenic knockout mouse, wherein the knockout mouse exhibits phenotypic changes that include lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold as compared to wild type mice.

The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that encodes a murine magnesium-dependent phosphatase gene wherein the disruption results in loss of function of the magnesium-dependent phosphatase. The specification does not teach how to make and use the invention with other species of transgenic or knockout animals and with any knockout mouse with any form of disruption in the gene encoding magnesium-dependent

phosphatase, as claimed in the claims 5-15, 17-23 and 45-52. Further, the specification does not teach how to make and use any cell comprising any type of disruption in a magnesium-dependent phosphatase gene as claimed. The scope of claims 5-10, 17-23 and thus surpasses that enabled by the specification.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention with any and all transgenic animals as claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two inactivated alleles for the gene that encodes a murine magnesium-dependent phosphatase wherein the knockout mice exhibit lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all transgenic animals and/or transgenic mice carrying any and all transgene(s) of the types recited in the claims.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification only discloses the phenotype of a homozygous magnesium-dependent phosphatase gene knockout mouse comprising a disruption in the

magnesium-dependent phosphatase gene but fails to disclose the phenotypes of any and all knockout animals with a disruption in magnesium-dependent phosphatase gene. Given the state of the art, the phenotype of any transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals, including mice, that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification.

Further, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). Thus, the disclosure, while being enabling for a homozygous knockout mouse containing two disrupted alleles for the gene encoding the magnesium-dependent phosphatase, does not provide sufficient support to predict the same phenotype in other animal systems.

The particular genetic elements required for expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, the phenotype of knockout animals is not predictable. For example, Jacks et al. (1992) describe Rb knockout mice that do not display retinoblastoma; rather they exhibit the unexpected phenotype of pituitary tumors. The pituitary tumors arise from cells lacking a wild-type Rb allele. Thus, tumors were found to arise not in retinas, as in humans, but in the pituitary gland (page 299, Discussion, paragraphs 1 and 3). Therefore, in the absence of specific guidance and working examples, the phenotype of transgenic animals with the scope as claimed is unpredictable. In such a situation, one skilled in

the art would not know how to make and use the invention as claimed, without undue experimentation.

The specification fails to provide an enabling disclosure for the preparation of other species of knockout animals besides mice having a disruption in the magnesium-dependent phosphatase gene because the guidance offered in the specification is limited to the preparation of mice harboring such mutations and no teachings or guidance are offered in regard to how one would have prepared any other type of animal having the recited gene disruption. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out the method. The prior art does not teach the generation of a transgenic mouse from any other types of cells. The only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. S38, column 1, paragraph 1). Thus, knockout animals cannot be prepared for any species other than the mouse. Since ES cell technology was required to produce the claimed animals and practice the claimed methods of using such animals, in the

absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals and to practice the claimed methods in species other than mice.

In view of the limited guidance in the specification, and limited working examples directed to transgenic, knockout mice with a specific knockout gene and exhibiting a specific phenotype, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to make and use the invention in its full scope as claimed. Thus, the enabled scope of the claims is limited to a homozygous knockout mouse comprising a disruption in the magnesium-dependent phosphatase gene, wherein no functional magnesium-dependent phosphatase is produced, and exhibiting phenotypic features of lung abnormality, elevated white blood cells, increased anxiety and increased pain threshold as compared to wild type mice, and a method of producing such a transgenic mouse.

Claims 1-10, 17-23 and 45-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, No. 4, pp. 1099-1111 (also available at www.uspto.gov).

The specification does not provide or point to a written description of the genus of magnesium-dependent phosphatase genes recited in the claims. The claims encompass a transgenic and/or knockout mouse containing a magnesium-dependent phosphatase gene

disruption. However, the specification only describes a single species of a magnesium-dependent phosphatase gene, the murine gene of SEQ ID No:1. The specification fails to teach other types of magnesium-dependent phosphatase gene. In analyzing whether a written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the claims encompass the whole genus of 'magnesium-dependent phosphatase genes' and include any and all transgenic animals that contain any altered allele for the gene that encodes a magnesium-dependent phosphatase. Thus for the claims to meet the written description requirement, other representative species of "magnesium-dependent phosphatase genes", should be described by their complete structure or by other relevant identifying characteristics, in the specification.

Next, then, it is determined if a representative number of species have been sufficiently described by other relevant identifying characteristics. In the instant case, no identifying characteristics are provided for the genus of magnesium-dependent phosphatase genes recited in the claims. Thus the limited information in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed genus of magnesium-dependent phosphatase gene disruptions. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus of "magnesium-dependent phosphatase genes".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 9, 10, 23 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-4, the term "selectable marker," "screening marker" or "selection marker" renders the claims indefinite because it is unclear how a marker protein can be part of a vector construct. It is recommended to use terms such as "selectable marker gene," "screening marker gene."

Regarding claim 2, the term "screening marker" renders the claim indefinite because the metes and bounds of the term are not clearly set forth. In other words, it is unclear how a "screening marker" differs from the "selection marker" recited in claim 1.

Regarding claims 1-4 and 10, it is unclear how the target construct is arranged. In other words, is the first polynucleotide adjacent to the second polynucleotide or there is a selectable marker in between? Where is the screening marker located in the construct? In addition, it is also unclear whether the first and second polynucleotide is a contiguous sequence of the target gene or just portions of the target gene. The arrangement of the elements is essential to the operability of the invention.

Regarding claims 9 and 23, the word "derived" renders the claim indefinite because the nature and number of derivative processes is unknown. Use of the term "isolated" is suggested.

Claim 52 recites the limitation "transgenic mouse" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claims 50 and 51 are drawn to a method of producing a transgenic mouse. Therefore, in the instance that claim 52 is depend on either 50 or 51, the limitation "transgenic mouse" lacks sufficient antecedent basis.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Kato et al. (1994, Gene, vol. 145, 311-312) and Travis et al. (1997, PNAS, vol. 94, 11055-11060).

The claims are drawn to a magnesium-dependent phosphatase gene-targeting construct and a method of making said construct. The claims are further drawn to a cell comprising a disruption in a magnesium-dependent phosphatase, and a method of producing a transgenic mouse comprising a disruption in a magnesium-dependent phosphatase gene by homologous recombination using the target construct.

Mansour et al. teach a strategy for targeted disruption of the hprt and proto-oncogene int-2 in mice embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cell carrying non-selectable, targeted gene mutation at loci of interest, and therefore provides a model which can be used to produce homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from hprt and

int-2 respectively, and a neo selection marker in between the two sequences (see page 350, figure 3). However, Mansour et al. do not teach how to make a magnesium-dependent phosphatase gene target construct and knockout mouse.

Kato et al. teach the cloning of a mouse magnesium-dependent phosphatase, MPPAα. They provide the cloned coding sequence for magnesium-dependent phosphatase gene (see page 312, figure 1).

Travis et al. teach that the human PP2Cα (magnesium-dependent phosphatase) dephosphorylates cystic fibrosis transmembrane conductance regulator (CFTR) *in vitro* (see page 11058, 1st col., 1st paragraph). Travis et al. also teach that PP2Cα reduces CFTR regulated Cl- current and increases the rate of channel inactivation *in vivo* (page 11058, 1st col., 2nd paragraph). Travis et al. further teach that these data and the finding that PP2C expresses abundantly in airway (see page 11057, Figure 2), an important site of cystic fibrosis pathogenesis, makes it a good target for developing inhibitors that has therapeutic value for cystic fibrosis (see abstract and page 11060, 1st col.).

It would have been obvious to one of ordinary skill in the art to make a magnesium-dependent phosphatase knockout construct to make a gene knockout mouse because of the combined teaching of Mansour et al., Kato et al. and Travis et al. The skilled artisan would have been motivated to knockout the expression of the magnesium-dependent phosphatase gene in a mouse to study the function of this gene and to develop specific inhibitors for this phosphatase which may useful in treating cystic fibrosis, as suggested by the teaching of Travis et al. The skilled artisan would have had reasonable expectation of success for making such a knockout mouse because of the teachings of Mansour et al., who teach a general method of targeted gene

disruption in mice based on homologous recombination using a cloned fragment of a desired gene, and Kato et al., who teach the coding sequence of the mouse magnesium-dependent phosphatase gene. Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 51-54 and 56 of copending Application No. 09,815,935. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to same transgenic mouse comprising a disruption in a magnesium phosphatase gene and exhibit phenotype of elevated white blood cell and pulmonary lesion.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER

Celine Qian, Ph.D.
December 13, 2002